REMARKS

I. Status of Claims and Formal Matters

Claims 11, 16-20, and 22 – 35 are pending in the application. No claim amendments or cancellations have been made herein. Applicants respectfully reserve the right to pursue any canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

II. The Rejections Under 35 U.S.C. § 103 Are Overcome

Claims 11, 16-20, 22-26 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yoji et al (Interaction of Intrathecally Infused Morphone and Lidocaine in Rats (Part I): Synergistic Antinociceptive Effects, *Anesthesiology*, December 1998, vol 89(6), 1455-1463. – "Yoji"), in view of Goodman and Gilman (*The Pharmacological Basis of Therapeutics*, seventh edition, 302-305 and 310-312 – "Goodman"), and in view of Elkhoury *et al.* (USPN 5589480 – "Elkhoury") in further view of Ptchelintsev *et al.* (USPN 5834513 – "Ptchelintsev"). Applicants respectfully disagree and traverse this rejection.

The present invention is directed to methods for topically providing synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject.

Yoji teaches the synergistic effects of morphine and lidocaine or bupivicaine when systemically administered via bolus injection or continuous coinfusion. Yoji does not teach the administration of butamben. Similarly, Yoji does not teach the topical administration of these compounds nor does Yoji suggest that the synergistic effect would be retained in the periphery via topical administration.

The synergistic administration of morphine and butamben for providing topical analgesia is alleged to have been prima facie obvious to one of ordinary skill in the art at the time of filing in view of the antinociceptive composition of Yoji, discussed above, in view of the mechanism of action of anesthetics described by Goodman in combination with Elkhoury, which teaches the use of morphine for providing topical analgesia, and Ptchelintsev, which teaches the use of butamben as a topical analgesic. The Examiner alleges that it would have been logical to

combine the teaching of these references given that the analgesic properties were each known individually in the art and their synergistic effect would have been expected.

It is respectfully submitted that the topical combination of morphine and butamben in the periphery produces a synergistic result that would have been unexpected to one of skill in the art of pain management at the time that the present application was filed.

It is alleged that lidocaine, bupivacaine and butamben all possess the same mechanism of action. As previously argued, Goodman teaches that lidocaine and procaine use the same generally accepted mechanism of action as local anesthetics and that benzocaine, an "ester-type" derivative of procaine, is similar to butamben picrate in its low aqueous solubility. Nevertheless, Goodman also teaches that lidocaine, unlike procaine and benzocaine, is an aminoacetamide (an amide-type anesthetic) and thus will react differently in patients than ester-type anesthetics owing to their different metabolic pathway (hydrolysis via plasma esterase and the liver versus hepatic endoplasmic reticulum).

The Examiner states "the metabolic properties of the individual compounds are irrelevant to the determination of the obviousness of synergism." Applicants respectfully disagree. Metabolic properties of a compound are most certainly relevant to a determination of the obviousness of synergism if such properties and/or pathways would bring about an effect that would be opposite to what one of ordinary skill in the art would otherwise expect. Moreover, any number of factors can play a role in the synergism of two compounds. Indeed, factors such as the previously discussed increased patient sensitivity and incidence of allergy to ester-type anesthetics could greatly effect the synergism of a proposed combination. Thus, even if one were to combine morphine and butamben in the method of Yoji, there would have been no expectation of success, as the synergistic effect may have been prevented by this metabolic pathway. Indeed, Yoji confirms this lack of expectation by concluding that "the nature of interaction may be altered depending on the type of opiod receptor subtype or local anesthetic."

Nevertheless, the teachings of Yoji are limited to providing a systemic antinociceptive effect in the central nervous system that cannot be extrapolated to a

local antinociceptive effect in the periphery. Prior to the teaching in the instant application, the importance of peripheral mechanisms in the mediation of antinociceptive responses was unknown. Opioid analgesia, for example, was largely perceived to be mediated through the central nervous system (i.e., systemically) and not necessarily through the opioid receptors located at peripheral sites. Those skilled in the art did not appreciate the significance of opioid stimulation at peripheral sites, much less the significance of combining opioid analgesics and local anesthetics at these peripheral sites. The synergistic potentiation of pain relief that occurs in the periphery when opioid analgesics are administered together with local anesthetics was unexpected given the state of the art.

In fact, several medical reports published before the filing of the present application teach that methods comprising the topical use of morphine fail to stimulate peripheral sites (all documents referred to herein are supplied on the Information Disclosure Statement accompanying this response):

For example, Raja *et al.* (Anesthesiology 77:1143-7; 1992) describe a randomized, double-blind study comparing the analgesic efficacy of bupivacaine and morphine administered intraarticularly in 47 patients having undergone arthroscopic knee surgery. The analgesic efficacy of the treatments was determined up to 72 hours following surgery by postoperative pain scores (VAS) and the amount of supplemental opioid required by each patient. A first group of patients received 20 ml of normal saline with 100 µg of epinephrine. A second group received 20 ml of 0.25% bupivacaine and 100 µg of epinephrine. A third group received 3 mg of morphine and 100 µg of epinephrine in 20 ml of normal saline (15% morphine). All medicaments were administered by injection into the joint space of the knee via an 18-G needle following arthroscopic surgery.

Raja *et al.* did not find any analgesic effect and/or activation of opioid receptors in the periphery as a result of intra-articular morphine administration. For example, the authors state on page 1146 that their study "fails to demonstrate functional opiate receptors in the knee joint in a clinical model of acute injury." Further, the authors conclude on page 1146 "that no evidence for a peripheral opiate-receptor mediated analgesia could be demonstrated in patients undergoing arthroscopic knee surgery under epidural anesthesia."

Rosenstock *et al.* (Ref. Anesth. 21:93-8; 1996) describe a double-blind, randomised, placebo-controlled study to evaluate the possible immediate and long-term analgesic effect of morphine injected incisionally in patients undergoing minor abdominal surgery (inguinal herniotomy). Following surgery, the patients were divided randomly into one of four groups. The first group received 5 mg of morphine (in 6 ml of saline; 83% w/v) infiltrated in the edges of the surgical wound. The second group received 5 mg of morphine (in 6 ml of saline; 83% w/v) injected in the subcutaneous layer of the surgical wound. The third group received 5 mg of morphine intravenously. The fourth group (placebo) had 6 ml of saline injected in the edges of the surgical wound. Any resulting analgesia was assessed with visual analog scale (VAS) scores over the course of 7 days following the operation. Further, the dosage and frequency of supplemental analgesics (acetaminophen and morphine) required by each patient was considered. However, Rosenstock *et al.* did not find any difference in analgesic effect among the four groups. That is, the placebo group (group 4) provides statistically the same level of analgesia as the three groups having been administered morphine. Similarly, the results did not show any statistical differences between the group in VAS scores nor did the groups show any statistical difference in the postoperative consumption of acetaminophen, alfetanil, or fentanyl. The authors conclude on page 96 that "neither an immediate nor delayed postoperative analgesic effect of incisional morphine could be demonstrated..." in the study.

Picard *et al.* (Pain 72:309-18; 1997) reviewed 26 randomized controlled trials ("RCT") carried out from 1987 through 1996, each directed at understanding whether an analgesic effect could be attained through activation of peripheral opioid receptors. In total, the 26 RCTs studied 925 patients, of which 485 received an opioid, including morphine, fentanyl, alfentanil, buprenorphine and butorphanol. The efficacy of the peripherally-applied analgesics was tested using a variety of surgical methods and analgesic administration methods, including intrapleural, intraperitoneal, incisional, and dental injections, perineural blocks, and brachial plexus sheath injections.

In reviewing the results and conclusions reached by the primary authors of each study to assess the evidence for peripheral opioid analgesia, the current authors

conclude in the abstract that none of the studies provided "evidence for a clinically relevant peripheral analgesic efficacy of opioids in acute pain." Picard *et al.* argue that the results of the 26 RCTs reviewed were either unequivocally negative (i.e., lacking support for peripheral opioid analgesia) or that the results were not clinically relevant. The current authors further state on page 316 that the primary authors "tended to over-interpret their findings and to confuse statistical significance with clinical relevance. Inattentive or uncritical readers [of the studies] may be misled into a false perception of treatment efficacy." Further, the current authors conclude on page 316 that the "clinical use of peripheral opioids requires much more evidence than we have at present."

Yarussi et al., (Reg. Anesth. Pain. Med. 24:142-5; 1999) describe a study to evaluate the post-operative analgesic effects, if any, of incisionally-administered morphine in patients undergoing lumpectomies and axillary node dissections in the treatment of breast cancer. The study was carried out in a double-blind, placebo-controlled fashion and involved 45 patients. Prior to surgery, each patient was put under general anesthesia. The patients were then randomized into 3 groups: a first group wherein the surgical site was irrigated for 5 minutes with a 6% solution of morphine sulphate (6 mg in 100 ml of buffer); a second group wherein the 6% solution of morphine sulphate (6 mg in 100 ml of buffer) was administered by intramuscular injection; and a third group wherein the surgical site was irrigated with a placebo (100 ml of buffer) for 5 minutes. Analgesia was assessed by using a visual analog scale card (VAS), supplemental opioid (e.g., fentanyl) consumption, and incidences of side-effects. The authors did not detect any analgesic effect in any morphine-administered group relative to the placebo group. The authors conclude on page 144 that they are "unable to demonstrate any analgesic benefits after topical administration of morphine [at the surgical site]."

Furthermore, Applicants invite the Examiner's attention to the declaration of Sandra C. Roerig, Ph.D., editor for the Journal of Pharmacology and Experimental Therapeutics ("the Journal") submitted in related application No. 09/975,812, now patent No. 6,790,855. (Copies of the declaration and its exhibits are attached hereto as Exhibit A). The data contained in the '855 patent was published in the Journal. Dr. Roerig attested to the May 19, 2000 statements of reviewers for the Journal who

in the ordinary course of business analyzed the data of the '855 patent (e.g., depicting the synergistic effect of topical compositions of morphine and lidocaine in mice) and found the results to be unexpected. In particular, one of the reviewers further stated that ***studies of this kind had "never been performed previously."*** Prior to the teaching of the present application, morphine and lidocaine were not known to synergistically potentiate the antinociceptive effects of each other ***in the periphery***. The extent to which they interact in the periphery, as first shown by the Applicants, was stated to be ***"profound" and "quite marked"*** by those skilled in the art.

In light of this, one of ordinary skill in the art, at the time of the invention, would not have had an apparent reason to utilize a combination of morphine and butamben topically based on the systemic teaching of Yoji and the mechanistic descriptions of Goodman.

Similarly, there is no motivation to combine Yoji and/or Goodman with Elkhoury and Ptchelintsev. As discussed above, Elkhoury and Ptchelintsev describe the topical administration of morphine and butamben, respectively. Although the topical anesthetic properties of each of morphine and butamben are disclosed by these references, there is no expectation of their synergistic effect in the periphery. Yoji does not rectify this deficiency as the synergistic effect described systemically by Yoji would not be anticipated when administered topically as discussed above.

As such, even if the Examiner is correct that "the metabolism of compounds having the same mechanism of action is useful here only in the determination of an optimal compound for use", one of ordinary skill in the art, at the time of the invention, would not have had an apparent reason to utilize a combination of morphine and butamben topically, let alone in such a way as to expect a synergistic effect on peripheral sites independent of a complete systemic effect.

Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103 are respectfully requested for claims 11-13, 16-26, and 33.

Claims 27-32 are rejected under 35 U.S.C. § 103 as being unpatentable over Yoji, Goodman, Elkhoury and Ptchelintsev as applied to claims 11-13, 16-26, and 33 above, and further in view of Mayer et al. (USPN 5,840,731 – "Mayer") Claims 34-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Yoji,

Goodman, Elkhoury and Ptchelintsev as applied to claims 11-13, 16-26, and 33 above, and further in view of Soo et al. (USPN 5,028,595 - Soo). Applicants respectfully disagree and traverse these rejections.

As stated above, the pending claims are directed to methods for topically providing synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject. As discussed in detail above, claims 11-13, 16-26, and 33 are nonobvious in view of the combination of cited references. Claims 27-32 and 34-35 ultimately depend from claim 11. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Moreover, the further combination of either Mayer or Soo with the combination of Yoji, Goodman, Elkhoury and Ptchelintsev fails to teach or suggest topical synergism between morphine and butamben in the periphery. Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103 are respectfully requested for claims 27-32 and 34-35.

CONCLUSION

In view of the remarks made herein, Applicants respectfully submit that the application is in condition for allowance and request favorable reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance are respectfully requested. Applicants urge the Examiner to call the undersigned at the telephone number below if a phone interview would be useful in expediting further prosecution of the application.

Respectfully submitted,

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APPENDIX A